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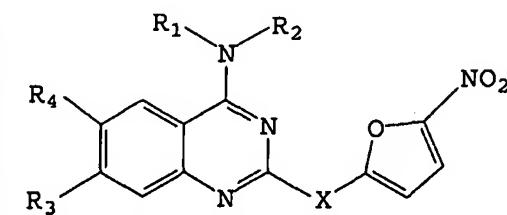
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(54) Title: HALOGENATED QUINAZOLINYL NITROFURANS AS ANTIBACTERIAL AGENTS



(I)

(57) Abstract: The present invention includes novel compounds of the formula (I) wherein X is absent or trans or cis CHCH, R<sub>1</sub> is (C<sub>1</sub>-C<sub>10</sub>) alkyl unsubstituted or substituted by one to three hydroxy, (C<sub>1</sub>-C<sub>10</sub>) alkenyl unsubstituted or substituted by one to three hydroxy, (C<sub>1</sub>-C<sub>10</sub>) alkynyl unsubstituted or substituted by one to three hydroxy, or aryl unsubstituted or substituted by one to three hydroxy; R<sub>2</sub> is hydrogen, alkyl or aryl; R<sub>3</sub> and R<sub>4</sub> are, independently of each other, H, halogen, or

a solubilizing group, with the proviso that at least one of R<sub>3</sub> and R<sub>4</sub> is halogen; and pharmaceutically acceptable salts thereof. The invention also includes pharmaceutically acceptable formulations of said compounds which exhibit antibiotic activity against a wide spectrum of microorganisms including organisms which are resistant to multiple antibiotic families and are useful as antibacterial agents for treatment or prophylaxis of bacterial infections, or their use as antiseptics, agents for sterilization or disinfection.

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Halogenated Quinazolinyl Nitrofurans as Antibacterial Agents

**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of United States Provisional Patent Application No. 60/493,336 filed 5 August 8, 2003, which is incorporated herein by reference.

**FIELD OF THE INVENTION**

This invention relates to novel nitrofuran antibiotics and their use for the treatment or prophylaxis of bacterial infections in humans or animals, or their use 10 as antiseptics, sterilizants or disinfectants. These compounds exhibit antibiotic activity against a wide spectrum of microorganisms, including organisms which are resistant to multiple antibiotic families.

**BACKGROUND OF THE INVENTION**

15 The following review of the background of the invention is merely provided to aid in the understanding of the present invention and neither it nor any of the references cited within it are admitted to be prior art to the present invention.

20 Management of nosocomial or community-acquired bacterial infections is becoming very difficult due to the emergence of bacteria resistant to one or multiple families of antibiotics. Unfortunately, the widespread and indiscriminant use of antibiotics has led to a rapid 25 increase in the number of bacterial strains which are resistant to antibiotics. Most importantly, resistance has emerged among clinically important microorganisms which threaten the utility of the currently available arsenal of antibiotics. A global trend of increasing resistance to

antibiotics, with wide variations according to geographical areas, is well documented by the World Health Organization and in the scientific literature.

There is a need for novel and effective  
5 antibiotics that are particularly active against microorganisms which are resistant to currently available drugs. For example, resistance of bacteria causing urinary tract infections to trimethoprim-sulfamethoxazole,  $\beta$ -lactams and fluoroquinolones is becoming a major factor in the  
10 management of such infections. Despite the use of nitrofuran antibiotics for several decades, mainly for the treatment of urinary tract infections, resistance to agents of this family has remained low (0-2%) in microorganisms most commonly encountered (Gupta K. Addressing antibiotic  
15 resistance. Dis Mon. 2003 Feb; 49(2):99-110; Nicolle LE. Urinary Tract Infection: Traditional pharmacologic therapies. 2003. Feb; 49(2):111-128).

United States Patent Nos. 3,970,648, 3,973,021 and 3,974,277 disclose nitrofurans of the following  
20 formulae: 2-[2-(5-nitro-2-furyl)vinyl]-4-(anilino)quinazoline, 2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline, 2-[2-(5-nitro-2-furyl)vinyl]-4-(o-hydroxyanilino)-quinazoline, and 2-[2-(5-nitro-2-furyl)vinyl]-4-(m-hydroxyanilino)-quinazoline. These  
25 patents teach the use of these compounds as pesticides and animal growth promotants for improving feed efficiency in animals such as poultry, swine and cattle. Although these molecules gained the property of being adequate edible feed additives for animal growth promotion compared to  
30 quinazoline molecules having the nitrofuran group directly attached to it (United States Patent No. 3,542,784), a drawback of the compounds from the above patents (Nos.

3,970,648, 3,973,021 and 3,974,277) is that the patents teach that they are now devoid of activity against important pathogens such as *Escherichia coli*, *Staphylococcus aureus* and *Salmonella*. It would be desirable to obtain nitrofurans 5 which provide significant improvement of potency and expand the antimicrobial spectrum of activity. This means that lower amounts of compounds are required for *in vitro* and *in vivo* (in animals) antimicrobial action against a wider variety of pathogens affecting animals and humans.

10        Besides, there are only a few nitrofuran antibiotics currently used in humans for the treatment of infectious diseases and one is known by the generic name nitrofurantoin (commercial names include: Macrobid, Macrodantin, Furadantin). It is used in adults and children 15 to treat acute urinary tract infections and to prevent recurrent urinary tract infections. A drawback of nitrofurantoin is that it does not have good potency (i.e., relatively high amounts are required to exert its antibacterial activity) and it does not have a wide spectrum 20 of antimicrobial activity, which limits the use of this compound in treating bacterial infections.

Novel nitrofurans with superior antimicrobial potency and improved pharmacological properties, would provide an alternative for the treatment of severe 25 infections caused by antibiotic-susceptible and -resistant microorganisms.

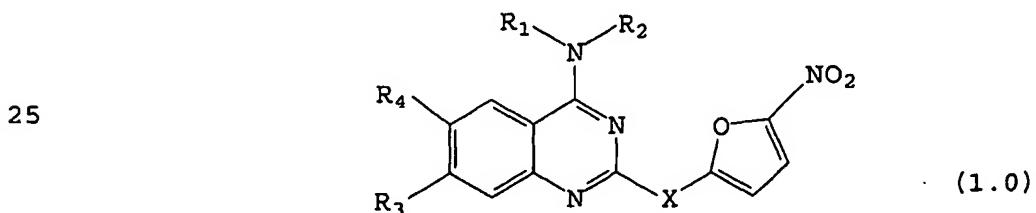
#### SUMMARY OF THE INVENTION

The compounds described herein can be used as antibiotics for the treatment or prophylaxis of bacterial 30 infections, or as antiseptics, sterilizants, or disinfectants.

The general structural feature of the compounds is a nitrofuran linked to the 2 position of a quinazoline directly or via a vinyl group. It is believed that the nitrofuran is essential for antimicrobial activity while the 5 quinazoline in particular as substituted, e.g., with an halogen and/or a methylpiperazino group, improves potency, expands the spectrum of activity (e.g., activity against *E. coli*, *S. aureus*, *Salmonella*, *Mycobacterium*, anaerobic bacteria and microorganisms that are resistant to multiple 10 antibiotics), provides a bactericidal (lethal) activity (i.e., as opposed to a bacteriostatic growth-inhibitory activity), provides *in vivo* activity, and improves solubility.

The quinazoline contains one or two functional 15 groups at the 4 position attached via an amine, and a hydrogen, halogen, or solubilizing group (such as an amine containing heterocyclic group, or more preferably an amine containing heterocyclic group which further contains at least one oxygen or nitrogen group) at the 6 or 7 position 20 with the proviso that at least one of the 6 or 7 positions are substituted with a halogen.

This invention includes compounds of the following general formula:



wherein

X is absent or trans or cis CHCH,

R<sub>1</sub> is (C<sub>1</sub>-C<sub>10</sub>)alkyl unsubstituted or substituted by one to three hydroxy, (C<sub>1</sub>-C<sub>10</sub>)alkenyl unsubstituted or substituted by one to three hydroxy, (C<sub>1</sub>-C<sub>10</sub>)alkynyl unsubstituted or substituted by one to three hydroxy, or

5 aryl unsubstituted or substituted by one to three hydroxy;

R<sub>2</sub> is hydrogen, alkyl or aryl;

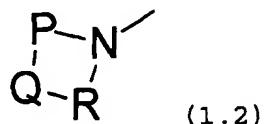
R<sub>3</sub> and R<sub>4</sub> are, independently of each other, H, halogen, or a solubilizing group,

with the proviso that at least one of R<sub>3</sub> and R<sub>4</sub> is

10 halogen;

and pharmaceutically acceptable salts thereof.

Preferably the solubilizing group is



wherein:

15 P and R are each independently selected from CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub> and CH<sub>2</sub>CHT where T is alkyl, and

Q is O, S, NH or NCH<sub>3</sub>.

The invention also includes pharmaceutically acceptable formulations of said compounds which exhibit

20 antibiotic activity against a wide spectrum of microorganisms including organisms which are resistant to multiple antibiotic families and are useful as antibacterial agents for treatment or prophylaxis of bacterial infections, or their use as antiseptics, agents for sterilization or

25 disinfection. In another aspect of the present invention there is provided compositions comprising the compounds of

the invention. In yet another aspect of the present invention there is provided processes for preparing the compounds of the invention. Certain terms that are used in this application are defined below.

5       The term "alkyl" refers to the radical of saturated aliphatic groups including straight chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. Typical alkyl groups include, but 10 are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, etc. The alkyl groups is preferably ( $C_1-C_{10}$ ) alkyl, and more preferably ( $C_1-C_6$ ) alkyl and even more preferably ( $C_2-C_4$ ) alkyl.

The term "alkyl" can encompass heteroalkyl groups 15 wherein one or more carbons of the hydrocarbon backbone are replaced with a heteroatom, e.g. N, O or S. The term "alkyl" can encompass a "substituted alkyl" having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, 20 for example, halogen, hydroxyl, carbonyl (such as carboxyl, ketones (including alkylcarbonyl and arylcarbonyl groups), and esters (including alkyloxycarbonyl and aryloxycarbonyl groups)), thiocarbonyl, acyloxy, alkoxyl, phosphoryl, phosphonate, phosphinate, amino, acylamino, amido, amidine, 25 imino, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety. The moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents 30 of a substituted alkyl may include substituted and unsubstituted forms of aminos, azidos, iminos, amidos, phosphoryls (including phosphonates and phosphinates),

sulfonyls (including sulfates, sulfonamidos, sulfamoyls and sulfonates), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF<sub>3</sub>, -CN and the like. Exemplary 5 substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxy, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF<sub>3</sub>, -CN, and the like. Any substituted alkyl may have 1 to 5 substituents or any combinations of 1 to 5 substituents.

10 The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, preferably (C<sub>2</sub>-C<sub>10</sub>), and more preferably (C<sub>2</sub>-C<sub>6</sub>) alkyl and even more preferably (C<sub>2</sub>-C<sub>4</sub>), but that contain at least one 15 double or triple bond respectively. An "alkenyl" is an unsaturated branched, straight chain, or cyclic hydrocarbon radical with at least one carbon-carbon double bond. The radical can be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are 20 not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobut enyl, tert-but enyl, pentenyl, hexenyl, etc. An "alkynyl" is an unsaturated branched, straight chain, or cyclic hydrocarbon radical with at least one carbon-carbon triple bond. Typical alkynyl groups include, but are not 25 limited to, ethynyl, propynyl, butynyl, isobutynyl, pentynyl, hexynyl, etc.

The term "aryl" refers to aromatic radicals having 3-14 ring atoms and at least one ring having a conjugated pi electron system. Preferably at least two, more preferably 30 at least four, of the ring atoms are carbon atoms. For example aryl may be a C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub> or C<sub>10</sub> ring. The term "aryl" encompasses "heteroaryl" compounds. The term

"heteroaryl" refers to an aromatic heterocyclic group usually with one or more heteroatoms selected from O, S and N in the ring. Examples of aryl include without limitation phenyl, substituted phenyl, pyridyl, substituted pyridyl,  
5 pyridinyl, substituted pyridinyl, thiophenyl, substituted thiophenyl, furanyl, substituted furanyl, thiazole, oxazole or substituted or unsubstituted imidazole. Such substituents can include, for example, halogen, hydroxyl, carbonyl (such as carboxyl, ketones (including alkylcarbonyl  
10 and arylcarbonyl groups), and esters (including alkyloxycarbonyl and aryloxycarbonyl groups)), thiocarbonyl, acyloxy, alkoxy, phosphoryl, phosphonate, phosphinate, amino, acylamino, amido, amidine, imino, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl,  
15 sulfonamido, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety. The moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted aryl may include substituted and unsubstituted  
20 forms of aminos, azidos, iminos, amidos, phosphoryls (including phosphonates and phosphinates), sulfonyls (including sulfates, sulfonamidos, sulfamoyls and sulfonates), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes,  
25 carboxylates, and esters), -CF<sub>3</sub>, -CN and the like. Such substituted aryl may have 1 to 5 substituents or any combinations of 1 to 5 substituents.

The term "halogen" refers to fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide or  
30 fluorine, chlorine, bromine or iodine.

The present invention includes the pharmaceutically acceptable salts of the compounds defined by general formula 1.0.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the invention which are substantially nontoxic to living organisms e.g. sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, hydrobromide, iodide, acetate, propionate, decanoate, caprate, caprylate, acrylate, ascorbate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, glucuronate, glutamate, propionate, phenylpropionate, salicylate, oxalate, malonate, succinate, suberate, sebacate, fumarate, malate, maleate, hydroxymateate, mandelate, mesylate, nicotinate, isonicotinate, cinnamate, hippurate, nitrate, stearate, phthalate, teraphthalate, butyne-1,4-dioate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, dinitrobenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, phthalate, p-toluenesulfonate, p-bromobenzenesulfonate, p-chlorobenzenesulfonate, xylenesulfonate, phenylacetate, trifluoroacetate, phenylpropionate, phenylbutyrate, citrate, lactate, alpha-hydroxybutyrate, glycolate, tartrate, hemitartrate, benzenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, hydroxyethanesulfonate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, 1,5-naphthalenedisulfonate, mandelate, tartarate and the like.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1. Time-kill curve for compound 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline (Compound V, Example I), compound 7-(4-methylpiperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline (Compound XV, Example VII) and ciprofloxacin against *S. aureus* ATCC 29213.

Figure 2. Time-kill curve for compound 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline (Example I, Compound V) and ciprofloxacin against *E. coli* ATCC 25922.

Figure 3. *In vivo* activity of compound 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline (Example I, Compound V) in a *S. aureus* model of systemic infection in the mouse.

**DETAILED DESCRIPTION**

Compounds of the present invention generally contain a nitrofuran linked to a quinazoline ring directly or by a vinyl group. The quinazoline ring contains one or two functional groups at the 4 position attached via an amine, a halogen at the 6 position or 7 position or both and at either the 6 position or 7 position, a hydrogen, a halogen or solubilizing group (such as an amine containing heterocycle or more preferably a heterocyclic containing at least one nitrogen and an oxygen or nitrogen group), and a nitrofuran moiety attached to the 2 position.

Compounds of the present invention can generally be made using the following methods. To 5-fluoro-anthraniamide hydrochloride is added, in steps, hydrochloric acid, acetic anhydride and aqueous ammonia,

forming 6-fluoro-2-methyl-4-(3H)quinazolinone. Next 5-nitro-2-furancarboxaldehyde is added with acetic anhydride and sulfuric acid to form 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(3H)quinazolinone (III), which is used to 5 prepare chloro and anilino derivatives. For example, phosphorus pentachloride and phosphorus oxychloride were added to form 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (IV) to which various functional groups can be added to the 4 position on the quinazoline. We refer 10 to the Examples for a more detailed description of these methods.

#### ANTIMICROBIAL DATA

Overview. *In vitro* and *in vivo* (in animals) tests have revealed the unique antimicrobial properties of 15 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline and derivatives, and demonstrated that the spectrum of activity of these molecules is highly suitable for treatment of difficult-to-treat human infections. In particular, 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline and 7-(4-methylpiperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline are highly potent broad-spectrum antibacterial agents that demonstrated activity against multiple Gram positive, Gram negative, acid-fast and anaerobic bacteria. 20 Such a property is comparable, or better, to extremely potent commercial drugs of the macrolide,  $\beta$ -lactam, or fluoroquinolone class. Moreover, the nitrofurans of the present invention like 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline and 25 7-(4-methylpiperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline, being of a different structural class, are not affected by commonly 30

found microbial mechanisms of resistance that have been developed over the recent years against most antimicrobial agents currently used clinically. Also, we were able to demonstrate that 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline, administrated by gavages, is active *in vivo* in a mouse model of infection, thus indicating oral bioavailability and relatively low toxicity. All these antimicrobial and chemical properties, represent those of a potent and safe antibiotic molecule.

10 In various embodiments, the nitrofurans of the present invention may be used therapeutically in formulations or medicaments to prevent or treat bacterial infections. The invention provides corresponding methods of medical treatment, in which a therapeutic dose of a  
15 nitrofuran of the present invention is administered in a pharmacologically acceptable formulation, e.g. to a patient or subject in need thereof. Accordingly, the invention also provides therapeutic compositions comprising a nitrofuran of the present invention, and a pharmacologically acceptable  
20 diluent, adjuvant, excipient or carrier. In one embodiment, such compositions include a nitrofuran of the present invention in a therapeutically or prophylactically effective amount sufficient to treat or prevent a bacterial infection. The therapeutic composition may be soluble in an aqueous  
25 solution at a physiologically acceptable pH.

A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, such as a reduction of bacterial infection. A therapeutically  
30 effective amount of a nitrofuran of the present invention may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of

the compound to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the 5 compound are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result, such as preventing or inhibiting the rate of bacterial infection- 10 related disease onset or progression. A prophylactically effective amount can be determined as described above for the therapeutically effective amount. For any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional 15 judgment of the person administering or supervising the administration of the compositions.

As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal 20 agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual 25 or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is 30 well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention

is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage.

- 5 The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid  
10 polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it  
15 will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for  
20 example, monostearate salts and gelatin. Moreover, a nitrofuran of the present invention can be administered in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound  
25 against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic  
30 acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are patented or generally known to those skilled in the art.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g. a nitrofuran of the present invention) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. In accordance with an alternative aspect of the invention, a nitrofuran of the present invention may be formulated with one or more additional compounds that enhance the solubility of the nitrofuran.

In accordance with another aspect of the invention, therapeutic compositions of the present invention, comprising a nitrofuran of the present invention, may be provided in containers or commercial packages which further comprise instructions for use of the nitrofuran for the prevention and/or treatment of bacterial infection.

Accordingly, the invention further provides a commercial package comprising a nitrofuran of the present invention, or the above-mentioned therapeutic composition, together with instructions for the prevention and/or treatment of bacterial infection.

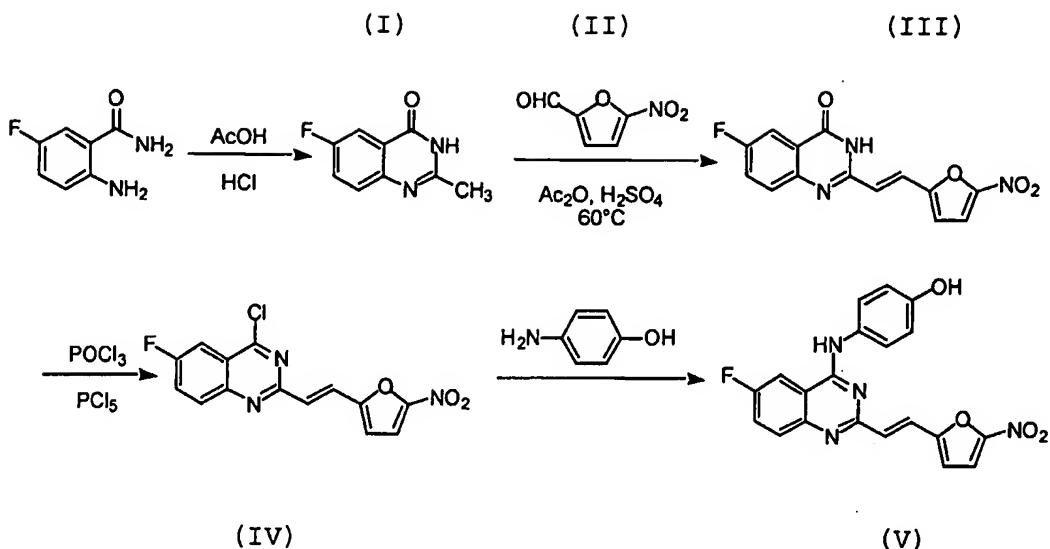
The invention further provides a use of a nitrofuran of the present invention for prevention and/or

treatment of bacterial infection. The invention further provides a use of a nitrofuran of the present invention for the preparation of a medicament for prevention and/or treatment of bacterial infection.

5       The invention further provides a use of a nitrofuran of the present invention as an antiseptic, sterilizant, or disinfectant.

Now in order to more particularly define some embodiments of the present invention, the following Examples 10 provide details of specific compounds of the invention, methods of producing the same and results from testing such compounds.

## EXAMPLE I

5 6-Fluoro-2-methyl-4-(3H)quinazolinone (I)

5-Fluoro-anthraniamide hydrochloride was prepared by adding 20 ml of concentrated hydrochloric acid (37% by weight) to a solution of 27.3 g of 5-fluoro-anthraniamide in 200 ml of methanol. This mixture was cooled in an ice bath to precipitate the hydrochloride which was then collected and dried to obtain a product. A 17.4 g (0.1 mole) portion of the hydrochloride thus obtained was refluxed for 3 hours with 100 ml acetic anhydride and allowed to stand overnight. The mixture was then cooled in an ice bath and the solids collected by filtration on a Buchner funnel. The filter cake was slurried in 100 ml of water, and warmed to enhance dissolution and then 28% aqueous ammonia was added until the mixture was alkaline. After cooling, the 6-fluoro-2-methyl-4-(3H)quinazolinone precipitated as a solid, was then collected, washed with a small amount of cold water and dried at 70°C to obtain the desired product.

5-nitro-2-furancarboxaldehyde (II)

A total of 86.5 g of 5-nitrofurfurylidine diacetate was added in small portions to 90 ml of sulfuric acid (73% by weight) over a period of 10 to 15 min. The mixture was stirred for 30 min at ambient temperature, 10 min at 50°C, cooled to 30°C, and then poured onto 150 g of crushed ice. The mixture was filtered, sucked as dry as possible on a Buchner funnel with the aid of a rubber dental dam and this afforded 51.5 g of 5-nitro-2-furancarboxaldehyde which melted at 32°-34°C.

6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(3H)quinazolinone (III)

To 16 g (0.1 mole) 6-fluoro-2-methyl-4-(3H)quinazolinone were added 100 ml acetic anhydride, 0.5 ml 15 96% sulfuric acid and 20 g (0.14 mole) 5-nitro-2-furancarboxaldehyde and the mixture was stirred 2 hours at 50°-60°C. The reaction mixture was poured into water and boiled 10 min. After it stood overnight, the product was collected by filtration, washed with water, then methanol. 20 A yellow solid was obtained. This solid 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(3H)quinazolinone was used to prepare the chloro- (IV) and anilino (V) derivatives described below.

6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (IV)

A 500 ml 3 necked flask fitted with a stirrer, reflux condenser and protected by a calcium chloride trap was charged with 9.0 g of phosphorus pentachloride (0.043 mole) and 70 ml of phosphorus oxychloride and the mixture stirred. To this 11.3 g (0.04 mole) of

6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(3H)quinazolinone was added and rinsed into the flask with 15 ml of phosphorus oxychloride. The mixture was heated under reflux for 4 hours, cooled in an ice bath and diluted with 150 ml of diethyl ether. The 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline which precipitated was collected by filtration, washed with 100-150 ml of diethyl ether, slurried in 100 ml of diethyl ether and then refiltered to obtain 8.09 g of the desired product.

10 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline (V)

A 250 ml Erlenmeyer flask equipped with a magnetic stirrer and oil bath for heating was charged with 8.0 g (0.07 mole) of p-aminophenol and 25 ml of dimethylformamide. 15 After the p-aminophenol was dissolved by stirring, (0.03 mole) of 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (IV) was added. The reaction mixture was then heated at 70°C-90°C for 2 hours after which 60 ml of water was added and the solution after cooling was placed in 20 a refrigerator for crystallization. After 3 days, the brown yellow solid was collected, washed first with water, then methanol and then dried to obtain 7.20 g of product.

**EXAMPLE II**

25 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(m-hydroxyanilino)-quinazoline (VI)

An Erlenmeyer flask is charged with 4.8 g (0.044 mole) of m-aminophenol and 100 ml of dimethylformamide. The charge is stirred to dissolve the m-aminophenol and 6.5 g (0.02 mole) of 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline 30 (IV) is added. The reaction mixture is reacted as in

Example I to obtain 6.5 g of crude product, a yellow solid which melts at 241°-242°C with decomposition. A 5.5 g sample is recrystallized from 40 ml of dimethyl formamide and 74 ml of methanol is added to the warm solution which is  
5 then cooled to recrystallize the purified product.

**EXAMPLE III**

6-fluoro-2-[2-(5-nitro-furyl)vinyl]-4-(o-hydroxyanilino)-quinazoline (VII)

An Erlenmeyer flask equipped with magnetic stirrer and oil  
10 bath for heating is charged with 5.0 g (0.046 mole) of o-aminophenol and 100 ml of dimethylformamide. The charge is stirred to dissolve o-aminophenol and 6.0 g (0.02 mole) of 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (IV) added. The reaction mixture is reacted at 80° to 90°C  
15 for 2 hours to form an organic precipitate; 100 ml of water is added to the warm mixture which is then allowed to cool and placed overnight in a refrigerator to crystallize. The solids are collected, washed with methanol and dried to obtain 7.5 g of brown-tan solid. A solution of the product  
20 in 100 ml of dimethylformamide is treated with activated carbon and filtered. A first portion of 75 ml of methanol is added to the warm filtrate then an additional 25 ml portion. Cooling and scratching gives 5.5 g of orange crystals of the purified product.

25 **EXAMPLE IV**

6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-anilinoquinazoline (VIII)

A 250 ml flask equipped with stirrer, reflux condenser and thermometer is charged with 4.1 g (0.044 mole)  
30 aniline and 100 ml dimethyl formamide. The charge is

stirred to dissolve and 6 g (0.02 mole) 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (IV) is added. The mixture is reacted at 130°-132°C for 2 hours to form a dark red solution. A 75 ml portion of water is added to the warm  
5 solution which is allowed to stand at room temperature overnight, then cooled 1 hour in an ice bath. The crystallized solid is collected, washed with methanol and dried to yield 5.5 g of brown solid. The solid is dissolved in 50 ml warm dimethyl formamide, decolorized with activated  
10 carbon, and precipitated by adding 100 ml methanol, with cooling and scratching to induce crystallization. The precipitated solid is collected and washed with methanol to yield the desired product.

#### EXAMPLE V

15 7-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-  
quinazoline (IX)

This compound is prepared in the same manner as 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline (example I) but starting with  
20 4-fluoroanthranilamine (27 g).

The synthesis of similar (non-nitrofuran) 6-halogenated quinazoline compounds is described in the following references.

Synthesis and histamine H<sub>2</sub>-antagonist activity of  
25 4-quinazolinone derivatives. Ogawa, Nobuo; Yoshida, Toshihiko; Aratani, Takayuki; Koshinaka, Eiichi; Kato, Hideo; Ito, Yasuo. Chemical & Pharmaceutical Bulletin (1988), 36(8), 2955-67.

Synthesis and biological evaluation of  
30 2-styrylquinazolin-4(3H)-ones, a new class of antimitotic

anticancer agents which inhibit tubulin polymerization.

Jiang, Jack B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *Journal of Medicinal Chemistry* (1990), 33(6), 1721-8.

5 Kuo, Sheng-chu; Hour, Mann-jen; Huang, Li-jiau; Lee, Kuo-hsiung. Preparation of 2-phenyl-4-quinazolinones and 2-phenyl-4-alkoxy-quinazolines as anticancer and antiplatelet drugs. U.S. (2002), 23 pp.

6-Alkylamino- and 2,3-Dihydro-3'-methoxy-2-phenyl-  
10 4-quinazolinones and Related Compounds: Their Synthesis,  
Cytotoxicity, and Inhibition of Tubulin Polymerization.  
Hour, Mann-Jen; Huang, Li-Jiau; Kuo, Sheng-Chu; Xia, Yi;  
Bastow, Kenneth; Nakanishi, Yuka; Hamel, Ernest; Lee,  
Kuo-Hsiung. *Journal of Medicinal Chemistry* (2000),  
15 43(23), 4479-4487.

**EXAMPLE VI**

6,7-Difluoro-2-Methyl-4-(3H)quinazolinone (X)

4,5-fluoro-Anthraniilamide hydrochloride was prepared by adding 10 ml of concentrated hydrochloric acid  
20 (37% by weight) to a solution of 10 g of 4,5-difluoroanthranilamide in 100 ml of methanol.

This mixture was cooled in an ice bath to precipitate the hydrochloride which was then collected and dried to obtain a product. A (0.01 mole) portion of the  
25 hydrochloride thus obtained was refluxed for 3 hours with 10 ml acetic anhydride and allowed to stand overnight. The mixture was then cooled in an ice bath and the solids collected by filtration on a Buchner funnel. The filter cake was slurried in 10 ml of water, and warmed to enhance  
30 dissolution and then 28% aqueous ammonia was added until the

mixture was alkaline. After cooling the 6,7-difluoro-2-methyl-4-(3H)quinazolinone precipitated as a solid, was then collected, washed with a small amount of cold water and dried at 70°C to obtain the desired product.

5 6,7-Difluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline (XI)

This compound was prepared in the same manner as that described in Example I or the synthesis of 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)quinazoline, 10 by using 6,7-difluoro-2-methyl-4-(3H)quinazolinone (1 g) as a starting material.

The synthesis of 4,5-fluoro-anthraniilamide is described in the following references.

15 Hayes, Thomas K.; Kiely, John S. Tricyclic tetrahydroquinoline derivatives and tricyclic tetrahydroquinoline combinatorial libraries. PCT Int. Appl. (1998), 119 pp. WO 9834111 A1 19980806.

20 Hayes, Thomas K.; Forood, Behrouz; Kiely, John S. 4-Substituted quinoline derivatives and 4-substituted quinoline combinatorial libraries. PCT Int. Appl. (1998), 124 pp. WO 9834115 A1 19980806.

25 Gao, Yun. Compositions containing N-amino- and N-hydroxy-quinazolinones and methods for preparing combinatorial libraries thereof. .S. (2001), 15 pp. US 6184377 B1 20010206.

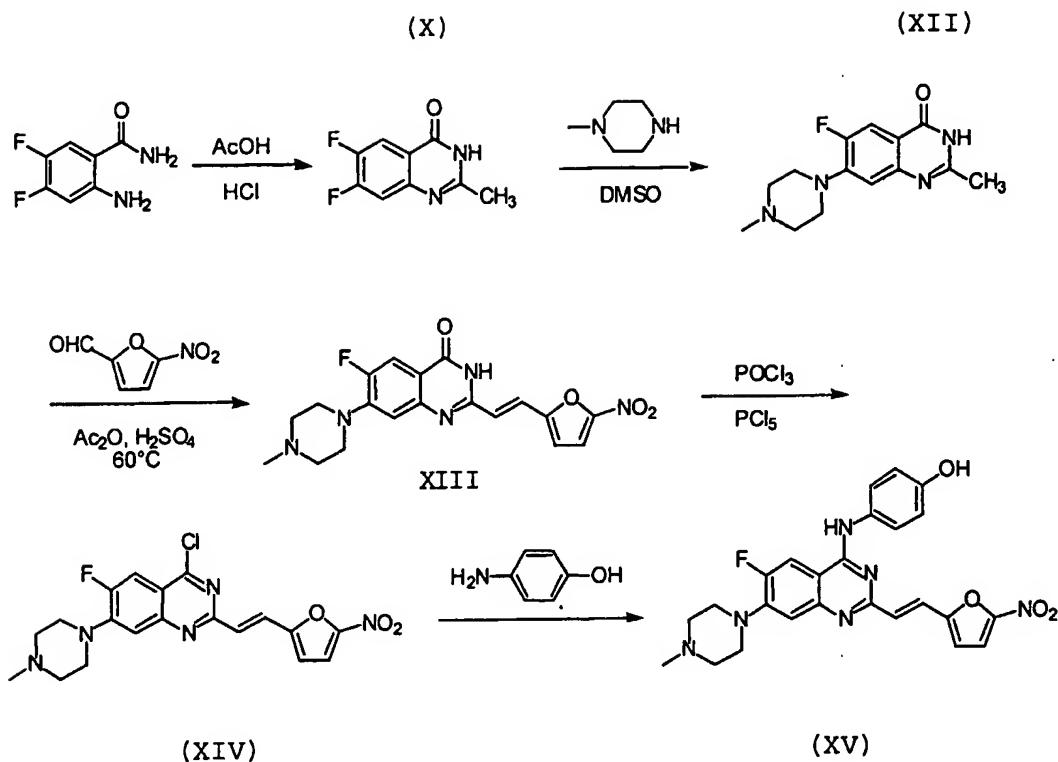
Desos, Patrice; Lepagnol, Jean M.; Morain, Philippe; Lestage, Pierre; Cordi, Alex A. Structure-Activity Relationships in a Series of 2[1H]-Quinolones Bearing Different Acidic Function in the

3-Position: 6,7 Dichloro-2[1H]-oxoquinoline-3-phosphonic Acid, a New Potent and Selective AMPA/Kainate Antagonist with Neuroprotective Properties. Journal of Medicinal Chemistry (1996), 39(1), 197-206.

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Sowell, C. Gregory; Kesicki, Edward A.; Oliver, Amy.  
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phosphatidylinositol 3-kinase delta. U.S. Pat. Appl. Publ.  
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Quinazolinone derivatives as inhibitors of human  
phosphatidylinositol 3-kinase delta. PCT Int. Appl. (2001),  
15 278 pp WO 0181346 A2 20011101.

## EXAMPLE VII



5   7- (4-methylpiperazino)-6-fluoro-2-Methyl-4- (3H) quinazolinone  
(XII)

To a solution of 6,7-Difluoro-2-Methyl-4-  
(3H)quinazolinone (X) (5 mmol) in DMSO (10 ml) was added  
4-methyl-piperidine (20 mmol). The mixture was heated to  
10 80°C for 4 h. After cooling water (30 ml) was added and the  
solid was collected by filtration. The product was further  
purified by flash chromatography.

7- (4-methylpiperazino)-6-fluoro-2-[2- (5-nitro-2-  
furyl)vinyl]-4-(3H) quinazolinone (XIII)

15   This compound was prepared in the same manner as  
described for 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-  
(3H)quinazolinone (III). Thus the desired product was  
obtained starting with XII (3 mmol).

7-(4-methyl piperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (XIV)

This compound was prepared in the same manner as described for 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline (IV). Thus the desired product was obtained starting with XIII (1.5 mmol).

7-(4-methylpiperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline (XV)

This compound was prepared in the same manner as described for 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxy-anilino)quinazoline (V). Thus the desired product was obtained starting with XIII (1.5 mmol).

**EXAMPLE VIII**

METHODS OF COMPOUND EVALUATION

15                   *Minimal Inhibitory Concentration (MIC)*

Determination. *Bacteria (primary strain panel, TABLE 1).*

Susceptibility tests were performed following the recommendations from the National Committee for Clinical Standards (NCCLS). The MICs were determined by a broth microdilution technique using a final volume of 100  $\mu$ l of cation-adjusted Mueller Hinton Broth (MHBCA) and a bacterial inoculum of  $10^5$ - $10^6$  Colony Forming Units (CFU)/ml. The inocula were verified and precisely determined by applying 10- $\mu$ l drops of 10-fold dilutions onto Triptic Soy Agar plates. The CFU were counted after an incubation of 24h at 35°C. Any experiment showing an inoculum that was more or less than  $10^5$ - $10^6$  CFU/ml was rejected. Control antibiotics and test compounds were prepared at a concentration equivalent to 2-fold the highest desired final concentration. Compounds were then diluted directly in the

96-well microtiter plates by serial 2-fold dilutions using a multichannel pipette. Microtiter plates were incubated during 24h at 35°C and growth was recorded by using a microtiterplate reader at 650 nm as well as by visual observation. The MIC was defined as the lowest concentration of compound yielding no visible growth. At least two commercial antibiotics (e.g., imipenem, ciprofloxacin, norfloxacin, nitrofurantoin, rifampicin, chloramphenicol, ampicillin, cefotaxime and vancomycin) were always included as internal microtiter plate controls in each MIC assay. Results from any microtiter plate that showed a discrepancy in such control antibiotic MICs compared to the NCCLS reference data for ATCC strains (a MIC differing by more than 2 doubling dilutions) were rejected.

15 **Fastidious bacteria.** The medium used for *Listeria monocytogenes*, *Neisseria meningitidis*, and *Campylobacter jejuni* was MHBCA containing 2% laked horse blood. The medium used for *Haemophilus influenzae* and *Branhamella (Moraxella) catarrhalis* was HTM as recommended by the NCCLS.

20 Cultures of these fastidious bacteria were incubated at 35°C in a 5% CO<sub>2</sub> atmosphere. The MHBCA medium used to grow *M. smegmatis* prior to the MIC assays was supplemented with 0.02% Tween-80 and results from microtiter plates were read after 48 hours of incubation. The medium used for

25 *Bacteroides fragilis* was Wilkins Chalgren broth and growth was allowed under an anaerobic atmosphere at 35°C for 48 hours.

Finally, compounds were also tested against populations of various clinical strains (antibiotic 30 resistant strain panel, TABLE 1).

TABLE 1. Strain panels used in the evaluation of antimicrobial activity of compounds.

Primary Strain Panel:

Gram positive.

*Staphylococcus aureus* ATCC 29213  
*Staphylococcus aureus* MRSA COL  
*Staphylococcus epidermidis* ATCC 12228  
*Staphylococcus saprophyticus* ATCC 15305  
*Enterococcus faecalis* ATCC 29212  
*Enterococcus faecium* ATCC 35667  
*Bacillus cereus* ATCC 11778  
*Bacillus subtilis* ATCC 6633  
*Bacillus atrophaeus* ATCC 9372  
*Listeria monocytogenes\** ATCC 13932

Gram negative.

*Escherichia coli* ATCC 25922  
*Escherichia coli* MC4100  
*Salmonella typhimurium* ATCC 14028  
*Acinetobacter baumannii* ATCC 19606  
*Yersinia enterocolytica* ATCC 23715  
*Haemophilus influenzae\** ATCC 49247  
*Haemophilus influenzae\** ATCC 49766  
*Branhamella (Moraxella) catarrhalis\** ATCC 8176  
*Campylobacter jejuni\** ATCC 33291

Anaerobic bacteria.

*Bacteroides fragilis\** ATCC 25285

Acid-Fast bacteria.

*Mycobacterium smegmatis\** ATCC 19420

Antibiotic Resistant Strain Panel:

10 *Staphylococcus aureus* MRSA  
8 *Escherichia coli*  
1 *Enterococcus faecium* VRE (*vanA*)

Note: \* = Fastidious bacterial species

**Minimal Bactericidal Concentration (MBC).** After the microtiter plates were read for the determination of the MIC, a 10- $\mu$ l sample of each clear well (at least 5 wells without visible growth) was applied onto TSA plates for 5 viable counts determination.

Petri dishes were incubated at 35°C for exactly 24h and bacterial colonies were counted. The MBC was the minimal concentration of antibiotic which resulted in 99.9% killing of the original inoculum. For example, if the 10 original inoculum was  $1 \times 10^6$  CFU/ml, the MBC was the concentration showing  $\leq 10$  colonies on TSA plate.

**Time-kill curves.** The bactericidal action of compounds was also evaluated over time (time-kill curve experiments). A bacterial inoculum of  $1 \times 10^5$  -  $1 \times 10^7$  15 Colony Forming Units (CFU)/ml was prepared. The inocula were verified and precisely determined by applying 10- $\mu$ l drops of 10-fold dilutions onto Tryptic Soy Agar plates. The CFU were counted after an incubation of 24h at 35°C. Any experiment showing an inoculum that was more or less 20 than the desired range of CFU/ml was rejected. Time-kill curve experiments were performed in 30 ml of MHB placed in 50-ml shaking flasks over a period of 24 hours. Test compounds and control antibiotics were added at time 0 hour and, at each time point, a sample was removed from flasks 25 and the CFU determined by plate counts as described above. CFU from compound-treated cultures were compared to CFU collected from the control flask without antibiotic. Test compounds and control antibiotics were assayed at the MIC or a multiple of the MIC as determined by a broth microdilution 30 technique as described above.

**In vivo efficacy.** The antimicrobial activity of compounds was also evaluated in a *S. aureus* model of systemic infection in the mouse. To produce the systemic infection, CD-1 female mice (20g) were injected intra-peritoneally with  $10^7$  CFU of *S. aureus* strain Newman suspended in 0.5 ml of endotoxin-free PBS containing 5% mucin (w/v). The compounds were administrated by oral gavage (15 mg/kg) at 1 hour post-infection and kidneys harvested and pooled, for each animal, 5 hours after bacterial inoculation. Tissues were homogenized in PBS and homogenates serially diluted and plated for CFU determination.

#### RESULTS OF COMPOUND EVALUATION

Inhibitory activity of Example I (compound V) and Example VII (compound XV). The compounds from Examples I and VII were evaluated against panels of microorganisms as described in TABLE 1 in order to determine their relative potency (MICs and MBCs) and breadth of spectrum. In the results outlined in TABLE 2, many reference microorganisms (American Type Culture Collection, ATCC strains) and many commercially available antibiotics were included in each of the tests used to characterize the activity of Examples I and VII in order to validate measurements and ensure high quality data.

TABLE 2. MICs (and MBCs) in µg/ml for control antibiotics and compounds of Examples I and VII obtained for a variety of Gram positive bacteria from the primary strain panel.

Antibiotic	<i>S. aureus</i> ATCC 29213	<i>S. aureus</i> MRSA COL	<i>S. epidermidis</i> ATCC 12228	<i>S. saprophyticus</i> ATCC 15305	<i>E. faecalis</i> ATCC 29212	<i>E. faecium</i> ATCC 35667
Example I compound V	0.03 - 0.06 (0.06)	0.015 (0.06)	0.03 (0.03)	0.015 - 0.03 (0.06)	0.03 (0.03)	0.06 (0.25)
Example VII compound XV	2	0.5	1 - 2	2	2 - 8	8
Ampicillin	1 - 2	8	64	0.12	1	1
Cefotaxime	1 - 2	512	0.5 - 1	8	2 - 8	16
Ceftriaxone	2	512	1	8	8	64
Chloramphenicol	16	8	8	4 - 8 (16 - 32)	8	8
Erythromycin	0.5	0.25	0.5	0.25	2 - 4	2
Furazolidone	4 - 16	8	2 - 4	2	8 - 16	>128
Gentamicin	0.5 - 2	0.5	0.06 - 0.25	0.06	4 - 16	4 - 16
Imipenem	0.015	16	0.008 - 0.015	0.03 (0.03 - 0.06)	0.5	2
Meropenem	0.06	16	0.06	0.25	2 - 4	16
Nitrofurantoin	16	16	16	8 (16)	8 - 16	64
Nitrofurazone	16	8 - 16	8	8	64	128
Norfloxacin	1	0.5 - 1	0.5	2 (4)	4	16
Oxacillin	0.12 - 0.25	512	0.12	1	8 - 16	32
Rifampicin	0.008 - 0.015	0.008 - 0.015	0.004 - 0.008	0.03	0.5 - 1	32
Tetracycline	0.5 - 1	2	128	1	16 - 32	0.5
TMP/SMX (1/19)	0.06/1.2	0.25/4.8 - 0.5/9.5	0.12/2.4 - 0.25/4.8	0.06/1.2 (0.25/4.8)	0.015/0.3	0.12/2.4
Vancomycin	0.5 - 2	1 - 2	1 - 2	1 (1)	2	0.5

Compound V and Compound XV showed exquisite activities against Gram positive bacteria generally causing severe opportunistic and/or nosocomial infections (TABLE 2). These included Methicillin-Resistant and Methicillin-  
5 Sensitive *S. aureus* strains [MRSA and MSSA, respectively], *S. epidermidis*, *E. faecalis* and *E. faecium*. The activity of Example I was better than that of imipenem, norfloxacin, vancomycin or several other commercial antibiotics against MRSA, *E. faecalis* and *E. faecium*. Compound XV was better  
10 than commercial nitrofurans like nitrofurantoin and nitrofurazone against all strains of TABLE 2.

Compound V was also very active against pathogens often causing urinary tract infections (e.g., *S. saprophyticus*, TABLE 2, and *E. coli*, TABLE 3). Against  
15 the reference strains, the activity of Compound V was better than commercial nitrofuran agents, like nitrofurantoin, usually used for treatment of urinary tract infections.

The MBCs of Compound V were most of the time equal to or only 2 to 4-fold higher than the MICs showing that  
20 this compound was bactericidal and not bacteriostatic.

Compound V also demonstrated a very good activity against three species of the bacterial genus *Bacillus* (i.e., *B. cereus*, *B. subtilis* and *B. atrophaeus*) with MICs ranging from 0.03 to 0.125 µg/ml (data not shown). *Bacillus*  
25 *anthracis*, the bacterial pathogen causing anthrax, is also a member of that bacterial genus.

Compounds V and XV showed excellent activity against respiratory tract pathogens causing community-acquired otitis media and pneumonia (TABLE 4). The activity  
30 of Compound V was superior to that of the β-lactam drugs (ampicillin, cefotaxime and meropenem) and macrolides

(erythromycin, clarithromycin) against *H. influenzae* ATCC 49247 and *B. catarrhalis*. Compounds V and XV were also very active against *Mycobacterium smegmatis* and their activity was superior to that of the commercial nitrofurans, 5 norfloxacin and rifampicin. *Mycobacterium tuberculosis*, the bacterial pathogen causing tuberculosis, is a member of that bacterial genus. Compound V was very active against *L. monocytogenes* and *C. jejuni* causing enteric infections and against *B. fragilis*, an anaerobe often causing difficult-to-10 treat abscesses and infections in diabetic patients.

TABLE 3 . MICs (and MBCs) in µg/ml for control antibiotics and compound of Example I obtained for a variety of Gram negative bacteria from the primary strain panel.

Compounds	<i>E. coli</i> ATCC 25922	<i>S. typhimurium</i> ATCC14028	<i>A. baumannii</i> ATCC 19606	<i>Y. enterocolytica</i> ATCC 23715
Example I compound V	0.5 (0.5)	1	1 - 2	0.25
Ampicillin	4 - 8	---	---	---
Meropenem	0.015-0.06	---	2	>0.5
Chloramphenicol	4 (16)	---	---	---
Cefotaxime	0.06 - 0.12	>2	16	>2
Imipenem	0.12	---	16	0.5
Ceftriaxone	0.03 - 0.06	---	---	---
Oxacillin	512 - >512	---	---	---
Erythromycin	64	---	---	---
Rifampicin	8	---	4	8
Norfloxacin	0.03 (0.06)	---	---	---
Tetracycline	1-2	---	16	>32
Gentamicin	0.5 - 2	---	32	2
Nitrofurantoin	8 (8)	32	128	64
Nitrofurazone	8-16	8	32	64
Furazolidone	1-2	2	32	>16
TMP/SMX (1/19)	0.25/4.75-0.5/9.5	---	8/152	0.125/2.4

TABLE 4. MICs (and MBCs) in µg/ml of control antibiotics and compounds of Examples I and VII obtained for Gram negative, Gram positive and acid-fast fastidious bacterial species.

Compounds	<i>H. influenzae</i> ATCC 49247	<i>H. influenzae</i> ATCC 49766	<i>B. catarrhalis</i> ATCC 8176	<i>M. smegmatis</i> ATCC 19420
Example I compound V	0.03 (0.06)	0.06 (0.06)	0.008 (0.03)	0.06
Example VII compound XV	2	2	0.5	0.25
Ampicillin	2-4 (4)	≤ 0.12 (< 0.12)	≤ 0.03 (<≤ 0.03)	---
Cefotaxime	0.12 (0.12)	0.008 (0.008)	0.03 (0.06)	---
Ciprofloxacin	0.008--0.015 (0.015)	0.008 (0.015)	0.03 (0.06)	---
Clarithromycin	16	128 (>128)	0.5 (1)	---
Erythromycin	2 (2)	8 (16)	0.06 (0.12)	---
Meropenem	0.06 (0.06)	0.03 (0.06)	0.002 (0.008)	---
Nitrofurantoin	---	---	---	64
Nitrofurazone	---	---	---	64
Norfloxacin	---	---	---	2
Rifampicin	---	---	---	8
Compounds	<i>L. monocytogenes</i> ATCC 13932	<i>C. jejuni</i> ATCC 33291	<i>B. fragilis</i> ATCC 25285	
Example I compound V	0.03 - 0.25	0.016	0.016	
Example VII compound XV	0.5	---	0.5	
Chloramphenicol	0.001	4	4	
Rifampicin	0.06	---	---	
Norfloxacin	0.008	---	---	
Tetracycline	---	0.5	0.25	
Imipenem	---	0.125	0.125-0.5	

The activity of Compounds V and XV was not influenced by the resistance mechanisms residing in multi-resistant *E. faecium* (e.g., strain VanA, TABLE 5). Similarly, the activity of Compounds V and XV was not influenced by the resistance mechanisms residing in multi-resistant MRSA strains (TABLE 6). This data was outstanding considering that at least 80% of the strains that were tested were resistant to many antibiotics of the conventional arsenal (e.g., oxacillin, erythromycin, norfloxacin).

The activity of Compound V was also not influenced by the resistance mechanisms residing in multi-resistant *E. coli* (e.g., strains Ec022c, Ec027c, Ec117c, Ec118c, and Ec119c, TABLE 7) or by the pathotype, i.e., the virulence characteristics of the strains (e.g., Enteroto-Hemorrhagic *E. coli* O157:H7 or Extra-Intestinal *E. coli* EIEC, TABLE 7).

The activity of Compounds V and XV against multi-resistant microorganisms, i.e., that are resistant to at least two structural classes of drugs, indicates that the chemical nature of the nitrofurans of the present invention was not previously encountered by such strains or did not elicit the development of resistance among these strains as opposed to all the other antibiotic classes that were tested (TABLES 5, 6, and 7).

TABLE 5. MICs in µg/ml of control antibiotics and compounds of Examples I and VII obtained for antibiotic multi-resistant *Enterococcus faecium* (VanA).

Compounds	<i>E. faecalis</i> ATCC 29212	<i>E. faecium</i> ATCC 35667	<i>E. faecium</i> VanA
Example I compound V	0.03	0.06	0.03
Example VII compound XV	2-8	8	0.5
Vancomycin	2	0.5	>128
Cefotaxime	2-8	16	>128
Clarithromycin	16	---	>128
Tetracycline	16-32	0.5	128
Rifampicin	0.5 - 1	32	>128
Furazolidone	8 - 16	>64	64
Nitrofurazone	64	>64	64

TABLE 6. MICs in µg/ml for control antibiotics and compounds of Examples I and VII obtained for a variety of antibiotic multi-resistant MRSA strains.

MRSA strains (n=10)	Example I compound V	Example VII compound XV	Oxacillin	Erythromycin	Norfloxacin	Gentamicin	Nitrofurantoin
MRSA COL	0.015	0.5	>128	0.25	1	0.5	8 - 16
Sa211c	<0.06	2	16 - 32	>32	>32	1	16 - 32
Sa212c	0.125	4	16	>32	>32	0.25	32
Sa220c	<0.06	0.25	8 - 16	0.5	>32	0.5	16
Sa224c	<0.06	1	32 - 64	>32	>32	0.25	16
Sa228c	<0.06	2	128	>32	>32	32	16 - 32
Sa234c	<0.06	2	32->128	>32	>32	1	16 - 32
Sa248c	<0.06	0.5	512	>128	32	>128	16
Sa249c	<0.06	0.5	512	>128	32	>128	16
Sa253c	<0.06	2	1024	>128	>128	>128	16

TABLE 7. MICs in µg/ml for control antibiotics and compound I obtained for a variety of antibiotic resistant *E. coli* strains and/or of different pathotypes.

<i>E. coli</i> strains (n=10)	Pathotype	Example I compound V	Ampicillin	Ciprofloxacin	Nitrofurantoin	TMP-SMX (1/19)	Tetracycline
ATCC 25922	Reference	0.5	4	0.03	8 - 16	0.25/4.75	-
MC4100	Reference	1	4	---	8 - 16	0.5/9.5	2
ATCC 35150	O157:H7	1	2	<0.25	2	0.03/0.6	---
d4-OLR-pen10	O157:H7	1	2 - 4	<0.25	16	0.125/2.4	>32
d25-ALR-pen14	O157:H7	1	2 - 4	<0.25	16	0.125/2.4	>32
Ec022c	EIEC	1	>64	0.015 - 0.03	16	>2/38	2
Ec027c	EIEC	1	>64	0.015	16	0.03/0.6	>32
Ec117c	EIEC	1	16	>128	8 - 16	>2/38	>32
Ec118c	EIEC	1	>64	64	16	>2/38	4
Ec119c	EIEC	2	>64	32	16	>2/38	>32

*Bactericidal activity of Compounds V and XV.*

Compound V of Example I and Compound XV of Example VII were evaluated in time-kill studies against *S. aureus* and/or *E. coli* (FIGURES 1 and 2, respectively). Results showed 5 that Compounds V and VII were strongly bactericidal within 2 hours against the tested strains. Compound V was superior to ciprofloxacin at their respective MIC or a multiple of the MIC against both species. Compound V was similarly bactericidal against strain *S. aureus* MRSA COL showing that 10 it is also able to kill bacteria resistant to commonly used antibiotics (data not shown).

*In vivo activity of Compound V.* Compound V was active *in vivo*. FIGURE 3 reports the results of a *S. aureus* peritonitis model of infection in the mouse. Results 15 clearly showed that Compound V reduced significantly the presence of viable bacteria in the kidneys. This important result demonstrated oral bioavailability of Compound V and its relatively low toxicity *in vivo*.

*Solubility of Compounds V and XV.* The extent of 20 solubility of compounds was evaluated in water. Compound V was soluble in water (no visible particles) at a concentration of 0.25 mg/ml, whereas Compound XV was 4 times more soluble (i.e., 1 mg/ml).

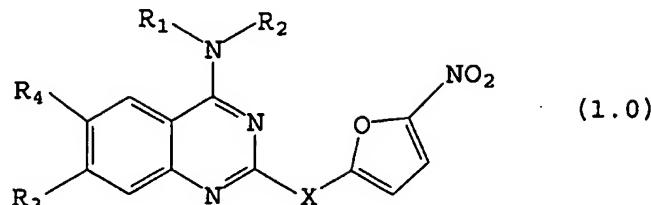
All patents, patent applications and publications 25 mentioned herein, both *supra* and *infra*, are hereby incorporated by reference.

While the invention has been described with reference to certain specific embodiments and will be described in the following Examples, it is understood that 30 it is not to be so limited since alterations and changes may

be made therein which are within the full and intended scope  
of the appended claims.

CLAIMS:

1. A compound of the formula



5

wherein

X is absent or trans or cis CHCH,

R<sub>1</sub> is (C<sub>1</sub>-C<sub>10</sub>)alkyl unsubstituted or substituted by one to three hydroxy, (C<sub>1</sub>-C<sub>10</sub>)alkenyl unsubstituted or 10 substituted by one to three hydroxy, (C<sub>1</sub>-C<sub>10</sub>)alkynyl unsubstituted or substituted by one to three hydroxy, or aryl unsubstituted or substituted by one to three hydroxy;

R<sub>2</sub> is hydrogen, alkyl or aryl;

R<sub>3</sub> and R<sub>4</sub> are, independently of each other, H, 15 halogen, or a solubilizing group,

with the proviso that at least one of R<sub>3</sub> and R<sub>4</sub> is halogen;

or a pharmaceutically acceptable salt thereof.

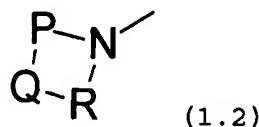
2. A compound according to claim 1, wherein R<sub>1</sub> is aryl 20 unsubstituted or substituted by one to three hydroxy and R<sub>2</sub> is hydrogen.

3. A compound according to claim 1, wherein R<sub>1</sub> is aryl substituted by one hydroxy and R<sub>2</sub> is hydrogen.

4. A compound according to any one of claims 1 to 3, 25 wherein R<sub>4</sub> is a halogen.

5. A compound according to any one of claims 1 to 3, wherein R<sub>4</sub> is fluorine.

6. A compound according to any one of claims 1 to 3, wherein the solubilizing group of  $R_3$  or  $R_4$  is



5

wherein:

P and R are each independently selected from  $\text{CH}_2$ ,  $\text{CH}_2\text{CH}_2$  and  $\text{CH}_2\text{CHT}$  where T is alkyl, and

$Q$  is O, S, NH or  $\text{NCH}_3$ .

10 7. A compound according to claim 6, wherein R<sub>3</sub> is a halogen and R<sub>4</sub> is partial formula (1.2) wherein Q is NH or NCH<sub>3</sub>.

8. A compound according to claim 6 or claim 7,  
wherein Q is NCH<sub>3</sub>.

15 9. A compound according to any one of claims 1 to 8,  
wherein R<sub>3</sub> is an amine containing heterocycle.

10. A compound according to any one of claims 1 to 8, wherein R<sub>3</sub> is N-methylpiperazine.

11. A compound according to any one of claims 1 to 10  
20 wherein X is trans CHCH.

12. A compound according to any one of claims 1 to 11, wherein R<sub>1</sub> is hydroxyethanol.

13. A compound according to any one of claims 1 to 11, wherein R<sub>1</sub> is hydroxyaniline.

14. A compound according to any one of claims 1 to 11, wherein R<sub>1</sub> is hydroxyphenyl.

15. A compound according to any one of claims 1 to 11, wherein R<sub>1</sub> is 2-hydroxyethanol.

5 16. A compound according to any one of claims 1 to 11, wherein R<sub>1</sub> is 4-hydroxyaniline.

17. A compound according to any one of claims 1 to 11, wherein R<sub>1</sub> is 4-hydroxyphenyl.

18. A compound according to any one of claims 1 to 17,  
10 wherein R<sub>2</sub> is phenyl, substituted phenyl, pyranyl, substituted pyridinyl, thiophenyl, substituted thiophenyl, furanyl, substituted furanyl, thiazole, oxazole or substituted or unsubstituted imidazole.

19. A compound according to claim 12 or claim 15,  
15 wherein R<sub>2</sub> is N-alkyl imidazole.

20. A compound of the formula 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-quinazoline.

21. A compound of the formula 7-(4-methylpiperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(p-hydroxyanilino)-20 quinazoline.

22. A compound of the formula 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline.

23. A compound of the formula 7-(4-methyl piperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-chloroquinazoline.

25 24. A compound of the formula 6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(3H)quinazolinone.

25. A compound of the formula 7-(4-methylpiperazino)-6-fluoro-2-[2-(5-nitro-2-furyl)vinyl]-4-(3H)quinazolinone.

26. A composition comprising a compound according to any one of claims 1 to 21.

5 27. A composition comprising a compound according to any one of claims 1 to 21, and a carrier, diluent or excipient.

28. A pharmaceutical composition comprising the compound according to any one of claims 1 to 21, and a 10 pharmaceutically acceptable carrier.

29. A method for treating a bacterial infection in a human or an animal, comprising administering to said human or said animal a therapeutically effective amount of a compound according to any one of claims 1 to 21, effective 15 in treating the bacterial infection.

30. A method of preventing a bacterial infection in a human or an animal, comprising administering to said human or said animal a prophylactically effective amount of a compound according to any one of claims 1 to 21 effective to 20 prevent the bacterial infection.

31. A method for disinfecting an object, including a human, of bacteria, comprising: contacting the object with the compound according to any one of claims 1 to 21 in an amount and for a time sufficient to achieve a desired degree 25 of disinfection.

32. A method of use of the compound according to any one of claims 1 to 21, for antisepsis of an object, including a human, of bacteria, comprising: contacting the object with the compound according to any one of claims 1 to

21 in an amount and for a time sufficient to achieve a desired degree of antisepsis.

33. A method for sterilizing a surface of an object, including a human, of bacteria, which comprises: selecting 5 an area of the surface for sterilization and applying the compound according to any one of claims 1 to 21, onto the surface of the object in an amount and for a time sufficient to achieve sterilization.

34. Use of the compound according to any one of 10 claims 1 to 21, in the manufacture of a medicament for treating or preventing bacterial infection.

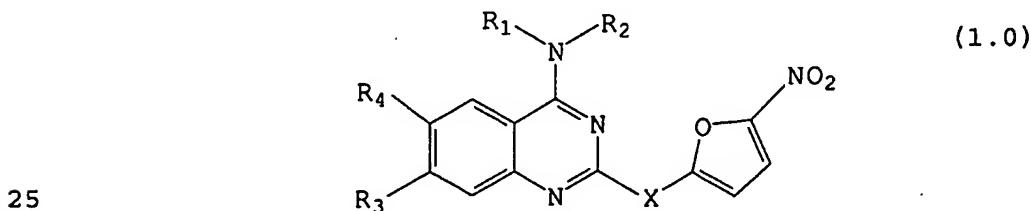
35. Use of the compound according to any one of claims 1 to 21, for treating or preventing bacterial infection in humans or animals.

15 36. Use of the compound according to any one of claims 1 to 21, for disinfection.

37. Use of the compound according to any one of claims 1 to 21, for antisepsis.

20 38. Use of the compound according to any one of claims 1 to 21, for sterilization.

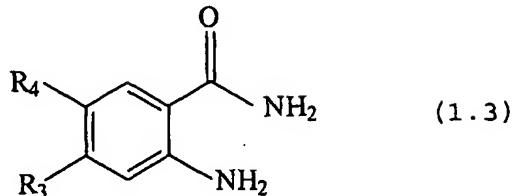
39. A process for the preparation of a compound of formula 1.0



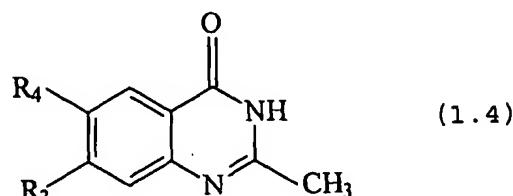
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in claim 1,

the process comprising:

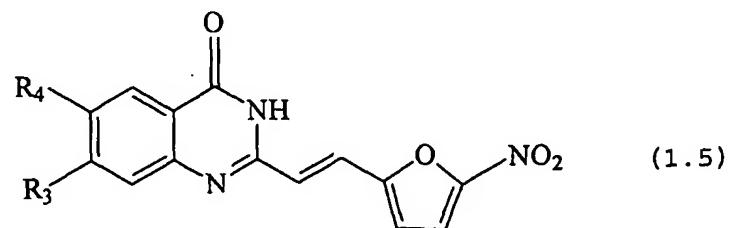
- a) reacting a compound of formula (1.3)



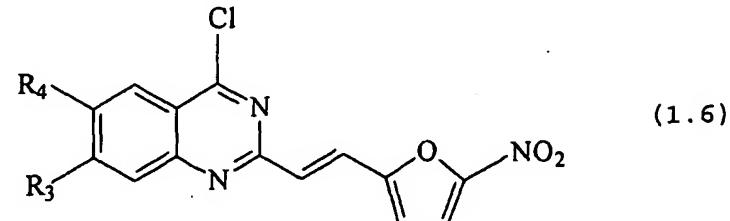
with hydrochloric acid, acetic anhydride and aqueous ammonia, to form a compound of formula (1.4)



- b) reacting the compound of formula 1.4 with 5-nitro-2-furancarboxaldehyde, to form a compound of formula (1.5)

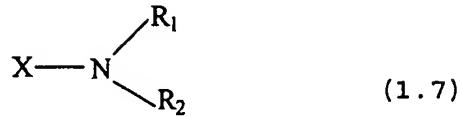


- c) reacting the compound of formula 1.5 with phosphorus pentachloride and phosphorus oxychloride to form a compound of formula (1.6)



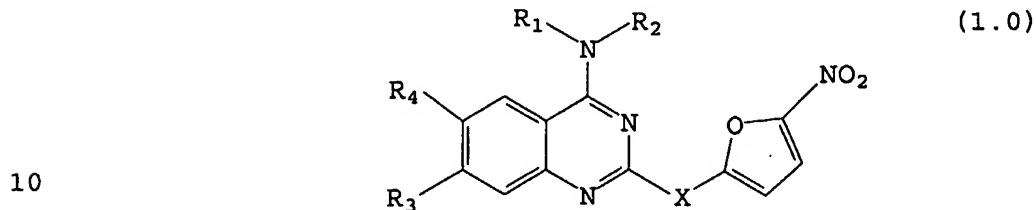
and

d) reacting the compound of formula 1.6 with a compound of the formula (1.7)



5 wherein X is H and R<sub>1</sub> and R<sub>2</sub> are as defined above.

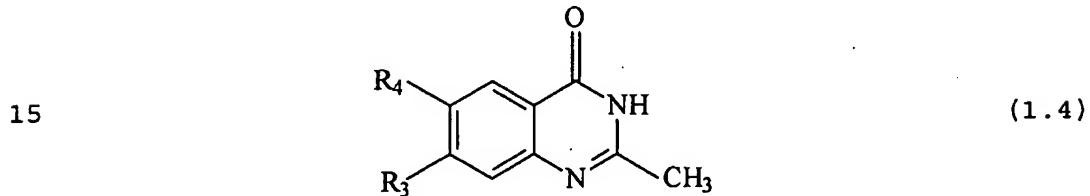
40. A process for the preparation of a compound of formula 1.0



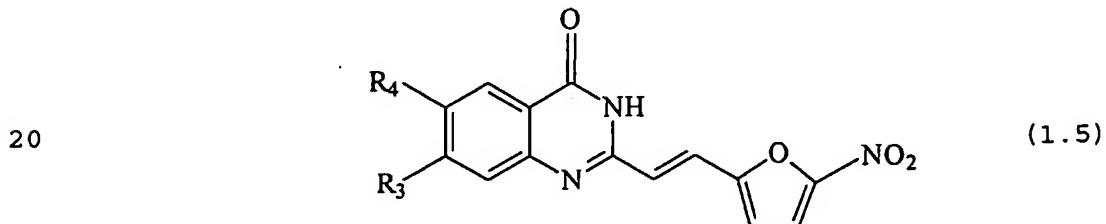
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in claim 1;

the process comprising:

b) reacting a compound of formula 1.4



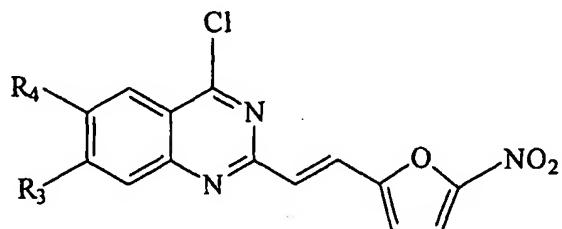
with 5-nitro-2-furancarboxaldehyde, to form a compound of formula (1.5)



c) reacting the compound of formula 1.5 with phosphorus pentachloride and phosphorus oxychloride to form a compound of formula (1.6)

5

(1.6)



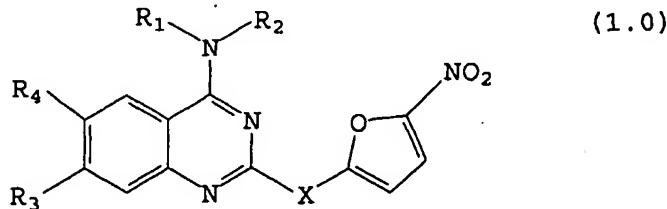
and

d) reacting the compound of formula 1.6 with a  
10 compound of the formula (1.7)



wherein X is H and R<sub>1</sub> and R<sub>2</sub> are as defined above.

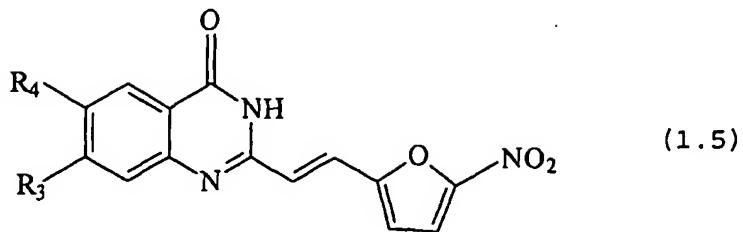
41. A process for the preparation of a compound of  
15 formula 1.0



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in claim 1,  
20 the process comprising:

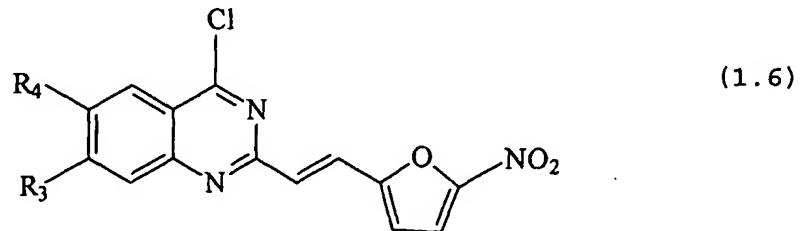
c) reacting a compound of formula 1.5

5



with phosphorus pentachloride and phosphorus oxychloride to form a compound of formula (1.6)

10



and

d) reacting the compound of formula 1.6 with a compound of the formula (1.7)

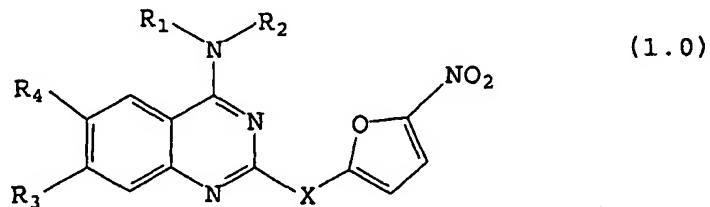
15



wherein X is H and R<sub>1</sub> and R<sub>2</sub> are as defined above.

42. A process for the preparation of a compound of formula 1.0

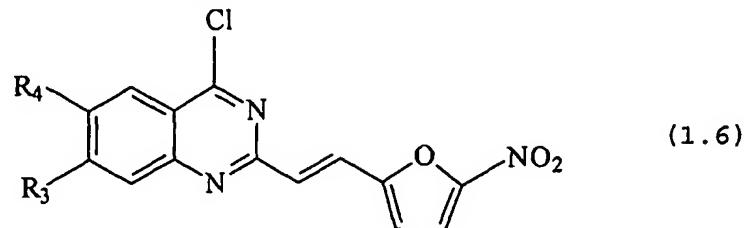
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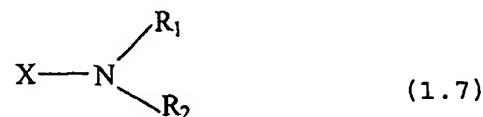
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined in claim 1,  
the process comprising:

d) reacting a compound of formula 1.6

5



with a compound of the formula (1.7)



10 wherein X is H and R<sub>1</sub> and R<sub>2</sub> are as defined above.

Figure 1. Time-kill curve for Example I (Compound V), Example VII (Compound XV), and ciprofloxacin against *S. aureus* ATCC 29213.

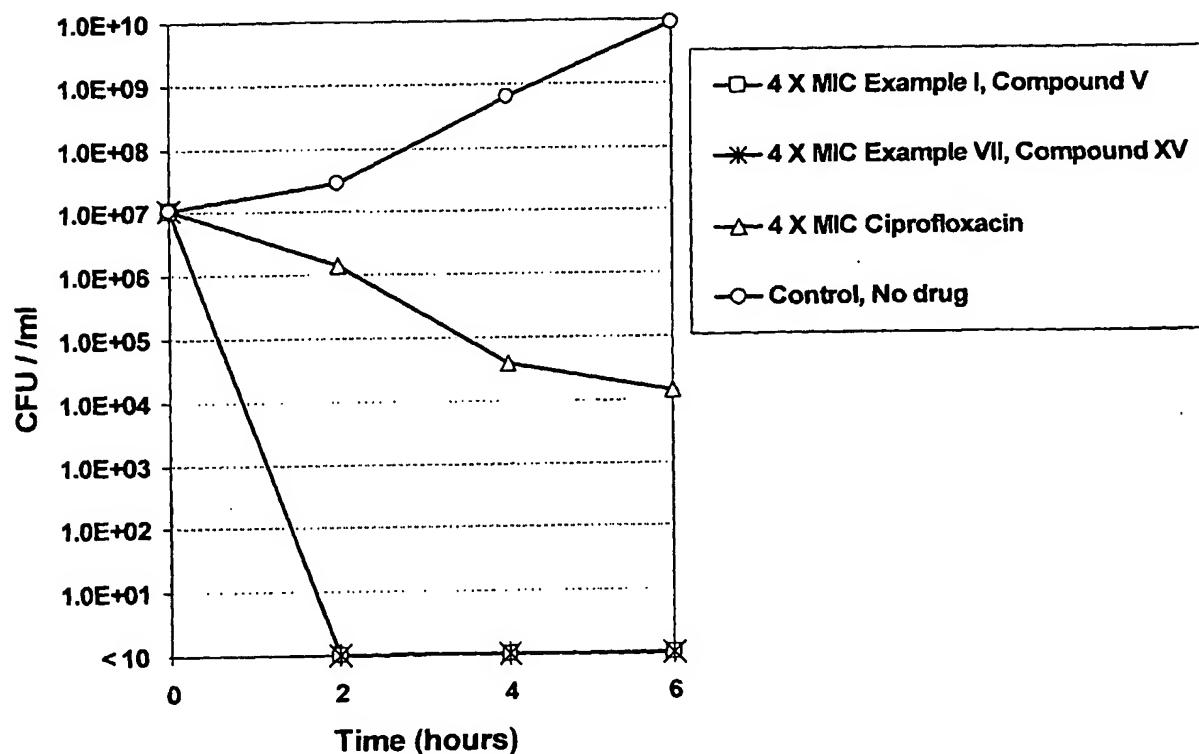


Figure 2. Time-kill curve for Example I (Compound V) and ciprofloxacin against *E. coli* ATCC 25922.

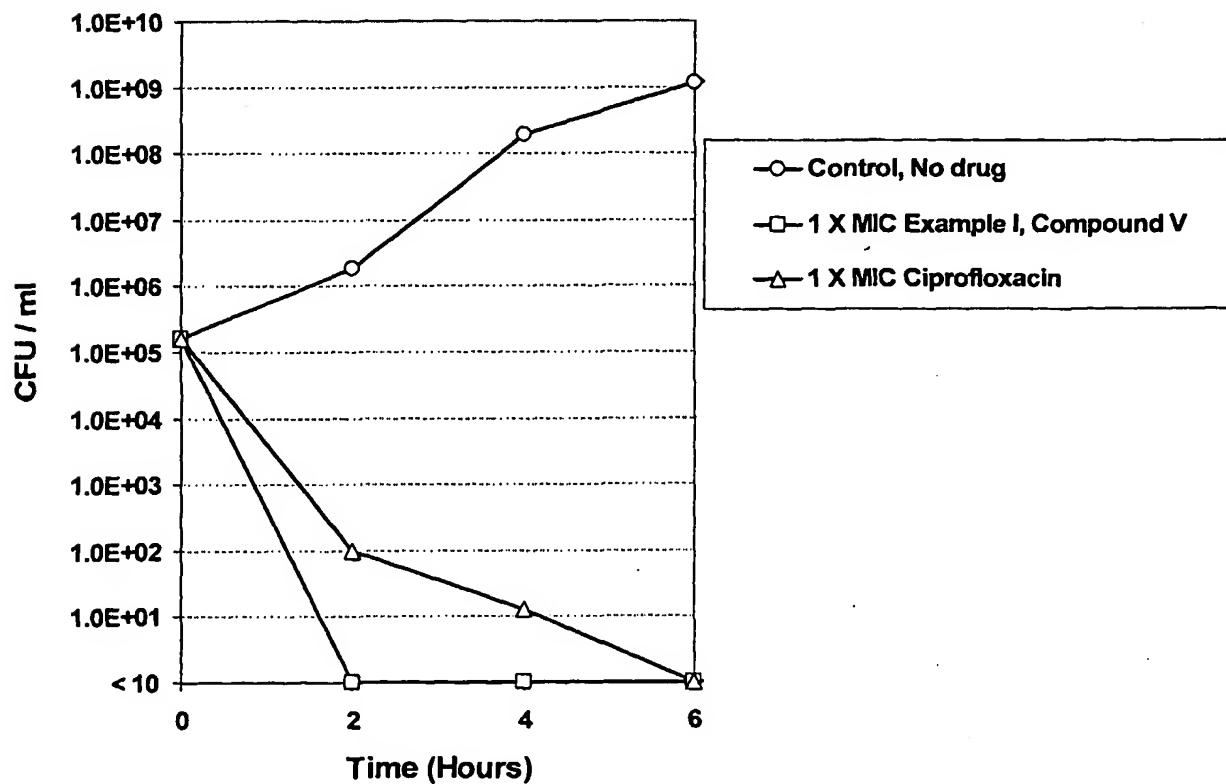
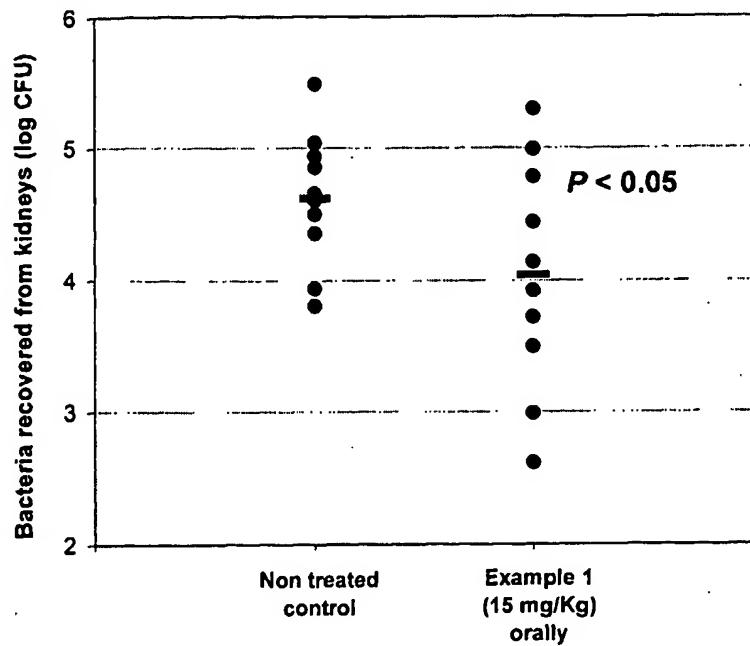


Figure 3. In vivo activity of compound Example I in a *S. aureus* model of systemic infection in the mouse.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2004/001466

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D405/04; C07D405/06; C07D405/14; C07D413/14; C07D417/14; A61K31/395

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D405/00; C07D413/14; C07D417/14; A61K31/395

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base, and, where practicable, search terms used)

Chemical Abstracts: structure search based on formula 1.2 of claim 6

US, WO, EP, CA full-text including OCR: IPC C07D405/, 413/14, 417/14 or A61K31/395 and keywords - nitrofuran plus related terms and antibacterial plus related terms

CA bibliographic data and image - CPC 167/212, 167/215, 167/217 167/218, 260/243, 260/244, 260/245, 260/253 and/or keywords - nitrofuran plus related terms and antibacterial plus related terms

Pluspat: ECLA/IPC C07D405/, 413/14, 417/14 or A61K31/395 and/or keywords - nitrofuran plus related terms and antibacterial plus related terms

MEDLINE: nitrofuran plus related terms and antibacterial plus related terms

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Zhikhareva G.P. et al, "Synthesis and Study of Antiviral Activity of Substituted 4-(d-diethylamino-a-methylbutylamino)-2-styrylquinazolines", Khimiko-Farmatsevticheskii Zhurnal (1978), 12 (11), 44. Chemical Abstracts: 90:121527	1, 11, 26-28
A	US 3970648 A (DIAMOND SHAMROCK) 20 July 1976 tables A and B, examples I-VI, claims (cited in the application)	1-42
A	US 3973021 A (DIAMOND SHAMROCK) 3 August 1976 tables A and B, examples I-VI (cited in the application)	1-42
A	US 3974277 A (DIAMOND SHAMROCK) 20 August 1976 tables A and B, examples I-VI, claims (cited in the application)	1-42
A	US 3542784 (NORWICH) 24 November 1970 the whole document (cited in the application)	1-42
A	US 3324122 A (NORWICH) 6 June 1967 the whole document	1-42

Further documents are listed in the continuation of Box C.

Patent family members are listed in annex.

* Special categories of cited documents :	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international-type search  12 November 2004 (12-11-2004)	Date of mailing of the international-type search report  17 December 2004 (17-12-2004)
Name and mailing address of the ISA/  Commissioner of Patents Canadian Patent Office - PCT Ottawa/Gatineau K1A 0C9 Facsimile No. 1-819-953-9358	Authorized officer  Yong-Huang Chen (819) 956-4113

Form PCT/ISA/210 (second sheet ) (January 2004)

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/CA2004/001466**Box No. II****Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1.  Claims Nos. : 29-33  
because they relate to subject matter not required to be searched by this Authority; namely:  
Although claims 29-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: 1-5, 9, 11-18 and 26-38 in part  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :  
Claims 1-5, 9, 11-18 and 26-38 lack clarity pursuant to Article 6 for being directed to the desired result rather than to the combination disclosed to achieve that result. The functional term "solubilizing group" in claim 1 is non-limitative and ill-defined in structure. It is uncertain what structural features are supposed to increase solubility. In view of the disclosed examples, the chemical structure search is therefore limited to formula 1.2 of claim 6.
3.  Claims Nos. :  
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III****Observation where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows :

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. :
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. :

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.  
**PCT/CA2004/001466**

Patent document cited in search report	Publication Date	Patent family members	Publication Date
US 3970648 A	20-07-1976	US 3973021 A US 3974277 A	03-08-1976 20-08-1976
US 3973021 A	03-08-1976	US 3970648 A US 3974277 A	20-07-1976 20-08-1976
US 3974277 A	20-08-1976	US 3970648 A US 3973021 A	20-07-1976 03-08-1976
US 3542784 A	24-11-1970	AT 284829B B BE 729298 A CH 507979 A DE 1909522 A1 DK 117566B B ES 363881 A1 FR 2005591 A5 GB 1168430 A IE 32904L L IL 31322 A NL 6904849 A NO 122373B B SE 357367 B	25-09-1970 03-09-1969 31-05-1971 30-10-1969 11-05-1970 01-01-1971 12-12-1969 22-10-1969 05-10-1969 30-05-1972 07-10-1969 21-06-1971 25-06-1973
US 3324122 A	06-06-1967	AT 255424B B BE 672504 A BR 6575667D D0 CH 448110 A DE 1620076 A1 DK 117902B B FR 1460221 A GB 1101179 A GB 1101180 A IL 24359 A NL 6513634 A NO 118066B B SE 325579 B	16-03-1966 06-09-1973 15-12-1967 12-02-1970 15-06-1970 17-06-1966 31-01-1968 31-01-1968 29-01-1969 15-06-1966 03-11-1969 07-07-1970